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Case Report

Undifferentiated necrotizing ulcerative vasculitis in a patient with pneumonia and stage 5 chronic kidney disease-a case report

Yulia Karpovich, Mehul Hitesh Sadadiwala*, Hardik Bakulkumar Mevawala, Fenilkumar Nitinbhai Ribadiya, Vladimir Bogdanovich

Department of Internal Medicine, Grodno State Medical University, Grodno, Belarus

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***Correspondence:**
Dr. Mehul Hitesh Sadadiwala,
E-mail: mevawalahardik@gmail.com

ABSTRACT

Skin is a frequently involved and damaged organ in cutaneous necrotizing vasculitis (CNV), mainly characterized histologically by a segmental angiocentric inflammatory condition with fibrinoid necrosis of the vessel wall. Various etiological factors have been described as probable causes that trigger CNV, ranging from infectious causes to autoimmune conditions. We have described a case of a middle-aged man with chronic kidney disease (CKD) that presented to the Grodno university clinic with *Staphylococcal pneumonia* and high level of the IgE antibodies that probably triggered CNV. Written consent was taken from the patient mentioned in the study. The study was approved by the hospital and institutional ethics committee. Based on the provisional diagnosis of hemorrhagic necrotizing vasculitis (cutaneous form), the patient was started on a low dose of glucocorticosteroid therapy. After carrying out a skin flap biopsy, a confirmed diagnosis of ANCA-negative CNV-leukocytoclastic vasculitis (LcV) form was made. The patient was started on steroid pulse therapy followed by plasmapheresis for elevated IgE count, leading to rapid resolution of symptoms. Literature has stated that CNV-LcV form commonly involves immune complexes composed of IgG or IgM. Based on our observation, we have proposed a novel hypothesis that elevated IgE and IgE immune complexes can be an additional triggering factor for CNV-LcV form as well.

Keywords: CNV, LcV, *Staphylococcus aureus*, IgE immune complexes

INTRODUCTION

Cutaneous necrotizing vasculitis (CNV) is a multisystem disorder generally involving the skin and mucous membranes (manifesting in numerous ways, commonly palpable purpura, and less frequently as urticarial or erythematous macules, papules, nodules, blisters, ulcers, or livedo reticularis), often accompanied by renal, gastrointestinal, pericardial, neurologic, and articular signs and symptoms.[1] CNV on histology is characterized by a segmental angiocentric inflammatory condition with fibrinoid necrosis of the vessel wall, inflammatory changes in endothelium, and perivascular nuclear dust (leukocytoclasia) of the post-capillary venules. The majority of biopsy specimens of CNV exhibit a small vessel neutrophilic vasculitis LcV that is commonly associated with immune complexes on direct immunofluorescence examination or, less commonly, antineutrophilic cytoplasmic antibodies (ANCA) by indirect immunofluorescence testing.[2] Often, cutaneous manifestations are observed and skin is to be the organ that is frequently involved and damaged, but systemic involvement may occur.[3]

There is considerable uncertainty due to the variability of its definition, the epidemiology of LcV varies with the underlying etiology. But the reported incidence of cutaneous LcV ranges from 15 to 38 cases per million/year, whereas the prevalence is from 2.7 to 29.7 per million.[4-6] 10% of affected patients are of pediatric demographic, mostly adolescent, and the age of onset of the disease as per the American College of

Rheumatology is after age 16.[3] Histologically, CNV is a segmental inflammation of venules, characterized by two main histologic patterns represented by the leukocytoclastic form LcV believed to be of immune complexes pathogenesis, and a lymphocytic form associated to cell-mediated immune responses.[1] The annual incidence of biopsy-proven LcV is approximately 45 individuals per million. LcV occurs in all ages and both genders; however, it typically presents in adults.[7] The histopathologic features are identical in most cases; however, there seems to be a subset of patients whose biopsy specimens show a predominantly neutrophilic infiltrate with few mononuclear cells. These patients have low levels of total serum complement and often have nephritis, arthritis, and deposits of immunoglobulin on the basement membrane zone of the epidermis. Another important histopathologic finding is the extent of vasculitis throughout the biopsy specimen because the depth of involvement seems to correlate well with the presence of more extensive and systemic vasculitis.[8]

Up to 60% of cases of CNV are of an idiopathic cause; in others, it may be due to a variety of underlying conditions such as infections, food allergens, chronic inflammatory systemic disorders, drugs, chemicals, or malignant neoplasms.[3,9-11] It can be associated with coexisting underlying diseases, trigger factors, precipitating events, or no other known cause. In patients with a drug-induced necrotizing vasculitis, the frequent causative agents included penicillin or erythromycin, thiazide diuretics, disulfiram, insecticide, clorazepate, or allopurinol. Whereas common infectious agents associated with necrotizing vasculitis are follows: *Streptococcus, Escherichia coli,* and *Staphylococcus aureus*. There is a wide spectrum of clinical presentations of necrotizing vasculitis, ranging from benign cutaneous lesions to full-blown systemic disease.[8]

The diagnosis of vasculitis is placed according to the 2012 CHCC (Chapel Hill consensus conference) classification, the following are required: (i) skin biopsy showing characteristic LcV and (ii) vasculitis limited to the skin.[12,13] In clinical practice, the isolated term "cutaneous LcV", may correspond to histological findings or descriptions, but this can be inaccurate, misleading, and non-specific. Most cases of isolated CNV are self-limited and attains resolution spontaneously over 3 to 4 weeks, most patients require no systemic treatment. For those with severe, intractable, or chronic and recurring vasculitis, systemic therapy may be indicated and should be adjusted as per the severity on an individual basis. Oral glucocorticoids may serve as a feasible option for a short duration in cases with the painful, ulcerative, or otherwise severe disease for resolution. Among drugs that are reasonable for longer-term use are colchicine, dapsone, azathioprine, or hydroxychloroquine.[14] Mainly the treatment is directed at the elimination of the cause. In other cases, local and systemic therapy is recommended after adequate laboratory screening.[15]

CASE REPORT

In the Autumn of 2022, a 36-year-old male patient with chronic nephritic syndrome and CKD 5 presents to the Grodno university clinic, with complaints of general weakness, swelling of the face and legs, and hemorrhagic rashes on the lower extremities. The patient has a prominent past medical history, dating back to early 2014 when he suffered from a perforated pre-pyloric ulcer of the stomach and widespread fibrinous-purulent peritonitis for which he underwent surgery. He also has a surgical history of laparotomy, splenectomy, and terminal ileostomy. In the past, the patient underwent reparative plastic surgery for a repair of a diaphragmatic hernia which was complicated by post-operative left-sided purulent pleurisy with pneumonia and sepsis. Due to postoperative complications, the condition of the patient deteriorated quickly leading to acute renal failure and hydronephrotic transformation of the left kidney with wrinkling. Since 2014, he has had repeated hospitalizations for perforation of ulcers, peritonitis, obstruction of the left lung, recurrent pneumonia, chronic tubulointerstitial nephritis, and glomerulonephritis.

In 2020, he was diagnosed with chronic nephritic syndrome, nephroangiosclerosis, hydronephrosis, and CKD 5 (GFR- 8 ml/min). Subsequently, a distal native arteriovenous fistula with auto-transplantation of a section of the saphenous vein was created and since then the patient had multiple sessions of hemodialysis.

In August of 2022, the patient complained about cough, shortness of breath, chest pain, and fatigue. After a thorough examination, the patient was hospitalized. Diagnostic procedures revealed right-sided hydrothorax of an unspecified etiology and secondary right-sided pneumonia with anemia of chronic disease. Pleurocentesis was done and the sample obtained showed 400ml of hemorrhagic fluid with clots. On CT-scan ground glass appearance with inflammatory changes was observed. The patient had no known antibiotic allergies or history of allergic reactions on exposure to antibiotics. He was treated accordingly with broad spectrum anti-biotics: meropenem 500 mg, cefepime 500 mg, levofloxacin 500 mg, sodiumchloride 0.9% solution, ambroxol 30 mg, enalapril 2.5 mg, analgin 500 mg, papaverin 150 mg q12hr, diphenhydramine 25 mg, omeprazole 40 mg, fragmin 5000 IU, bisoprolol 10 mg. The patient was discharged after the complete resolution of symptoms.

The patient returned to the clinic 15 days post-discharge, complaining of generalized weakness. The patient was re-admitted and a nares swab was withdrawn from which *Staphylococcus aureus* was isolated, seed rate- 10^6 coagulase-negative methicillin resistant-*Staphylococcus aureus* (MRSA) and Candida were isolated from the sputum. The overall condition of the patient deteriorated rapidly, the blood culture showed bacteremia and was further complicated by the development of bacterial

sepsis. He was treated for sepsis with Vancomycin 1g q12hr, fluconazole 200 mg, zopiclone 7.5 mg, omeprazole 40 mg, unfractionated heparin 5000 IU, epicim (human recombinant erythropoietin) 30 U/kg/dose, Ferrous fumarate 360 mg, folic acid 1 mg, losartan 50 mg, ketorol (ketorolac tromethamine) 10 mg, solupred (prednisolone) 5 mg. A few days after following the treatment for bacterial sepsis, the patient developed a high IgE antibody count, and ELISA showed elevated levels of IgE (1650.4 UI/ml, normal 150 to 1,000 UI/ml). IgA and IgG counts were high-normal, whereas IgM was found to be in the normal range. The patient developed hemorrhagic rashes with central foci of necrosis on the legs. A provisional diagnosis of hemorrhagic Necrotizing vasculitis (skin form) was made. ANCA and ANA tests were performed which turned out to be negative. Methylprednisolone 24 mg/day under the cover of his near conclusion antibiotic therapy for sepsis was prescribed with the continuation of antiplatelet therapy Aspicard (Aspirin) 325 mg q6hr.

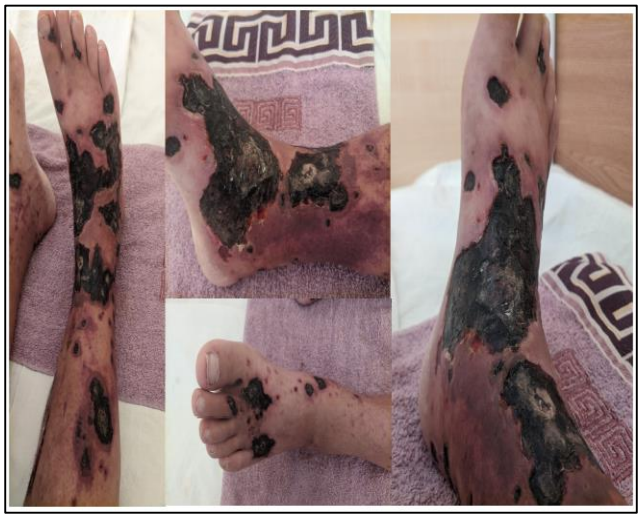

Figure 1: Male patient with CNV, LcV. Necrotic lesions on lower extremities, the size of necrotic lesions varied from 0.5 to 6 cm.

The patient developed intense itching on the shins and black necrotic scabs without improvement in the previous lesions. On local examination, feet and legs were warm to the touch. Pulsations were symmetrically present and both legs appeared to be swollen. The size of necrotic lesions varied from 0.5 to 6 cm (Figure 1) and a new single dense crusted lesion was isolated on the upper extremity as well. There were no symptoms of plantar ischemia.

The skin and subcutaneous tissue biopsy concluded the presence of LcV with characteristic histological features on skin flap biopsy, the decision on further treatment tactics needed the involvement of a rheumatologist, a vascular surgeon, and a hematologist. By this time the bacterial sepsis had already subsided and as there was an expansion of the necrotic zone, it was decided to increase the dose of glucocorticoids. He was put on pulse therapy-IV methylprednisolone 1000 mg for 3 days. The patient was also recommended to continue the treatment of other underlying diseases, and control of blood sugar levels, cholesterol, and blood pressure. Elevated IgE antibodies and IgE immune complex deposition was treated with FFP albumin plasmapheresis (one session) and anti-immunoglobulin sorption (2 sessions). The patient showed a rapid resolution of symptoms over a few days and was discharged. The patient was discharged with Methylprednisolone 24 mg/day with gradual tapering of the dose. He was recommended to continue his hemodialysis. On follow up, a month after his discharge the patient showed a significant healing of scars. Two months after his discharge the patient had completely healed scars and did not have any complaints with improvement in his general condition.

DISCUSSION

CNV has been shown in patients with chronic infections (viral, bacterial, protozoa, helminthic), a variety of auto-immune diseases (systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, Behcet's disease) hyperglobulinemic states, bowel bypass syndrome, cryoglobulinemia, ulcerative colitis, cystic fibrosis, cirrhosis, primary biliary and HIV infection.[10] Association with malignancies is not frequent. Lymphoproliferative disorders (Hodgkin's disease, lymphosarcoma, adult T-cell leukemia, multiple myeloma, mycosis fungoides) and solid tumors (lung cancer, colon carcinoma, renal, prostate, head and neck cancer, and breast cancer) may be associated with CNV.[15]

The diagnostic approach to LcV almost invariably requires a skin biopsy and should be focused to understand if it is skin-limited or systemic as the treatment is consequently different. In limited forms, eliminating the cause and using steroids are often sufficient, whereas systemic vasculitis therapy is based on corticosteroids, immunosuppressive agents, rituximab, or plasma exchange according to the extent and severity of the disease.[16] Whenever possible, treatment is directed at the elimination of the cause. In other cases, local and systemic therapy is recommended after adequate laboratory screening.[15]

The history of illness in our patient started with a *S. aureus* colonization and generalized infection which turned into sepsis. Zele et al reported on nasal colonization of *S. aureus*, causing a combined local immune response consisting of IgE formation and eosinophilic inflammation in most samples.[17] This *Staph*. colonization also led to IgE formation and a significant elevation of IgE levels, which was followed by the LcV form of CNV. *Staphylococcus aureus* and elevated IgE count can be precipitating factors for LcV in select individuals like our patient that had CKD which can cause delayed immune complex clearance and trigger LcV. The correlation of *Staphylococcus aureus* as an

etiological factor has been established before, and cases have shown that LcV can also be a sign of bacteriemia. Published literature has stated that LcV in which immune complexes are composed of IgG or IgM is more often limited to the skin and may additionally show minor systemic involvement.[18] But no cases of IgE immune complex-mediated LcV have been reported so far.

Patient was treated with high-dose corticosteroids (pulse therapy)-IV methylprednisolone 1000 mg for 3 days and plasmapheresis and anti-immunoglobulin sorption. After 1 session of plasmapheresis and 2 sessions of and anti-immunoglobulin sorption the patient showed a significant reduction in circulating IgE levels followed by rapid resolution of symptoms and improvement in overall condition. On subsequent follow ups within a month of discharge patient had no complaints and healing of necrotic scars was noted. Based on our observations and treatment outcomes of patient propose novel hypothesis that elevated levels of IgE can also be precipitating factor for LcV, especially in patients with CKD.

CONCLUSION

There are various factors that can trigger CNV, *Staphylococcal* infection is one such common causative factors. A middle-aged male patient with CKD presented to Grodno university clinic that went on to develop CNV secondary to elevated levels of IgE antibody. Elevated levels of IgE haven't been reported previously as a trigger for CNV, LcV form. Based on our observations and the treatment outcomes of the patient, we propose a novel hypothesis that elevated levels of IgE can also be a precipitating factor for LcV, especially in patients with CKD. High-dose corticosteroid therapy with plasmapheresis and anti-immunoglobulin sorption can be the mainstay treatment for aggressive manifestations of similar forms of necrotizing vasculitis.

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